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Short Communication

Low Frequency Association of the t(2;5)(p23;q35) Chromosomal Translocation with CD30$^+$ Lymphomas from American and Asian Patients

A Reverse Transcriptase-Polymerase Chain Reaction Study

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Although cytogenetic data suggest that the t(2;5)-(p23;q35) translocation occurs in many cases of CD30$^+$ lymphomas, the exact frequency of this event is still unknown. To clarify this issue and its epidemiological characteristics, we examined 37 formalin-fixed, paraffin-embedded specimens of CD30$^+$ lymphomas from the United States and Hong Kong by reverse transcriptase-polymerase chain reaction (RT-PCR) for the status of the NPM and ALK genes, which are typically juxtaposed by the t(2;5) translocation. Thirty-four cases were classified as anaplastic large cell lymphomas (ALCL), 2 cases as non-anaplastic large cell lymphomas (LCL), and 1 case as the small cell variant of CD30$^+$ lymphoma. The t(2;5) translocation was detected in 6 cases (16%), including 3 of 18 American patients and 3 of 19 cases from Hong Kong. All cases had a 185-bp NPM RT-PCR product as detected by Southern blot analysis, indicating adequate preservation of mRNA. The 6 positive cases were among 4 of 34 adult lymphomas, as compared with 2 of 3 childhood cases. Five of 17 T-lineage cases were t(2;5)-positive, compared with 1 of 15 B-lineage cases and none of the 5 null-cell or mixed lineage cases. Our results therefore show that t(2;5) occurs at a low frequency among CD30$^+$ lymphomas, at least in our adult-dominated series. (Am J Pathol 1995, 146:323–328)

A number of previous studies have reported the presence of a consistent chromosomal translocation involving the short arm of chromosome 2 and the long arm of chromosome 5, ie, t(2;5)(p23;q35), in cases of so-called "malignant histiocytosis" (MH).[1–4] Other studies have reported the same t(2;5) in cases of childhood phagocytic large T-cell lymphoma mimicking malignant histiocytosis.[5] Further studies provided evidence that some cases previously interpreted as malignant histiocytosis or regressing atypical histiocytosis were actually CD30$^+$ lymphoproliferations, often of T-cell lineage but also of B-cell or undetermined lineage.[6–10] Finally, several studies have documented a frequent association of t(2;5) with CD30$^+$ anaplastic large cell lymphomas (ALCLs) varying from 50 to 100%, and a strong association between t(2;5) and ALCL has been assumed.[11–18]

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On the other hand, a few studies appeared to indicate a weak association of t(2;5) with $CD30^+$ ALCL.[19] Moreover, the specificity of this t(2;5) has been questioned by several investigators who have also found it in $CD30^+$ non-anaplastic large cell lymphomas,[15,20,21] mixed cell lymphoma,[16] the small-cell variant of Ki-1 lymphoma,[17] and even in CD30-negative non-ALCL.[20] Furthermore, other chromosomal abnormalities such as complex hyperdiploid karyotype, 14q, 2p, and 6q abnormalities have been reported in anaplastic large cell lymphoma.[22,23] There is little data available on the cytogenetics of primary $CD30^+$ lymphomas in skin.

The true frequency of this translocation in $CD30^+$ lymphomas remains to be defined. Since the recent cloning of t(2;5), it is now possible to rapidly analyze $CD30^+$ lymphomas by reverse transcriptase-polymerase chain reaction (RT-PCR)[24] for the presence of t(2;5). In the current study, we examined 37 formalin-fixed, paraffin-embedded cases of $CD30^+$ lymphomas, mostly ALCLs, occurring in the United States and Hong Kong to determine how often t(2;5) is associated with $CD30^+$ lymphomas, and whether this association, if present, is correlated with other characteristics of these tumors.

Materials and Methods

Specimens

Thirty-seven formalin-fixed, paraffin-embedded specimens of $CD30^+$ lymphomas were analyzed. Eighteen specimens were retrieved from the combined archives of the Departments of Pathology of The City of Hope National Medical Center and the University of Virginia Health Sciences Center. Nineteen specimens were obtained from The Department of Pathology of Queen Elizabeth Hospital in Hong Kong. The clinicopathological characteristics and Epstein-Barr virus EBER-1 *in situ* hybridization results of all of the American cases and 14 of the Hong Kong cases have been recently published.[25]

RT-PCR Studies

A messenger RNA (mRNA)-based PCR method was used as previously described.[24] The mRNA was isolated (Invitrogen, San Diego, CA) and the RT-PCR reactions were performed according to the manufacturer's recommendations (Perkin-Elmer, Branchburg, NJ). In brief, RT-PCR reactions were performed simultaneously with oligonucleotide primers specific for the chimeric mRNA encoding for nucleophosmin and anaplastic lymphoma kinase (NPM-ALK) transcript (5′NPM: 5′-TCCCTTGGGGGCTTTGAAATAACACC-3′; and 3′ALK: 5′-CGAGGTGCGGAGCTTGCTCAGC-3′) and with a primer pair derived from the NPM gene as a control for reverse transcription and amplification of NPM mRNA (3′NPM: 5′- GCTACCACCTCCAGGGGCAGA-3′; and 5′NPM). Temperatures used during the 45 amplification cycles were 94 C for 60 seconds, 62 C for 60 seconds, and 72 C for 120 seconds. The 175-bp NPM-ALK fusion product was detected by hybridization with an end-labeled oligonucleotide homologous to sequences spanning the fusion junction (5′-AGCACTTAGTAGTGTACCGCCGGA-3′). The 185-bp NPM product was detected with an oligonucleotide homologous to normal NPM sequences (5′-GTGCTGTCCACTAATATGCAC-3′). Positive control consisted of a SUP-M2 cell line known to possess t(2;5),[10] and negative controls consisted of normal liver tissue.

Immunohistochemical Studies

Immunophenotypic studies were performed on formalin-fixed, paraffin-embedded sections using a previously published technique without modification.[26] Several antibodies reactive on routinely processed paraffin-embedded materials were used including monoclonal antibodies to CD45 (LCA, Dako, Carpinteria, CA), CD20 (L26, Dako), CD43 (Leu 22, Becton-Dickinson, San Jose, CA), CD45RO (UCHL1, Dako, or A6, Zymed laboratories, South San Francisco, CA), CD30 (Ber-H2, Dako), and epithelial membrane antigen (EMA, Dako).

Results

Clinicopathological and Immunophenotypic Characteristics

The clinicopathological and immunophenotypic data of all 18 American cases and 14 of the Hong Kong cases of ALCL have been previously reported.[25] The 5 additional Hong Kong cases included 3 childhood T-cell non-ALCLs and 2 adult ALCLs (one T-cell and 1 null lineage). Of these additional cases, one of the childhood cases was a primary cutaneous small cell variant $CD30^+$ T-cell lymphoma, and the two others were non-anaplastic large cell lymphomas (LCLs) involving the chest wall (1 case) and the neck (1 case). Cervical lymph node enlargement was the presentation in the two adult cases, and one of them also had nasopharyngeal involvement. Overall, there were 20 males and 17 females, with a median age of 50 years

(range: 8–82 years). Thirty-one cases were noncutaneous CD30+ lymphomas and 6 cases were primary cutaneous CD30+ lymphomas. No significant differences in sex, age, or site distribution between the Asian and American patients were observed. Immunophenotypically, 15 cases were of B-cell lineage, 17 cases were of T-cell lineage, 1 case expressed both B- and T-cell markers, and 4 cases were of null cell lineage.

RT-PCR Studies

RT-PCR studies indicated the presence of t(2;5) in 6 of 37 (16%) of CD30+ lymphomas as detected by agarose gel electrophoresis and confirmed on Southern blot hybridization by the presence of a 175-bp NPM-ALK fusion product (Figure 1). All of the cases tested had a positive 185-bp NPM product as detected by Southern blot (Figure 2), confirming the adequate preservation of viable RNA within the paraffin sections. The clinicopathological and immunophenotypic data of the 6 t(2;5)-positive cases are summarized in Table 1. χ^2 analysis with continuity correction was used to analyze the data. Three of 18 Americans and 3 of 19 Asian cases ($P = 0.70$) were positive for t(2;5). The t(2;5) translocation was detected in 4 of 34 adult cases and 2 of 3 childhood cases ($P = 0.09$). Four of 34 ALCL and 2 of 2 LCL were t(2;5)-positive ($P = 0.02$); the one case of the small cell variant of CD30+ T-cell lymphoma was negative for t(2;5). Five of 17 T-lineage cases and 1 of 15 B-lineage were t(2;5)-positive ($P = 0.23$); the 5 cases of null-cell or hybrid cell lineage were all negative. One of 4 cases previously demonstrated by us to be EBV-positive by EBER *in situ* hybridization had a detectable t(2;5), while 5 of 30 EBV-negative cases were t(2;5)-positive ($P = 0.73$).[25] Two of six primary cutaneous CD30+ lymphomas were t(2;5)-positive, and 4 of 31 noncutaneous CD30+ lymphomas were t(2;5)-positive ($P = 0.22$); interestingly, both of the cases of adult ALCL with splenic involvement were t(2;5)-positive.

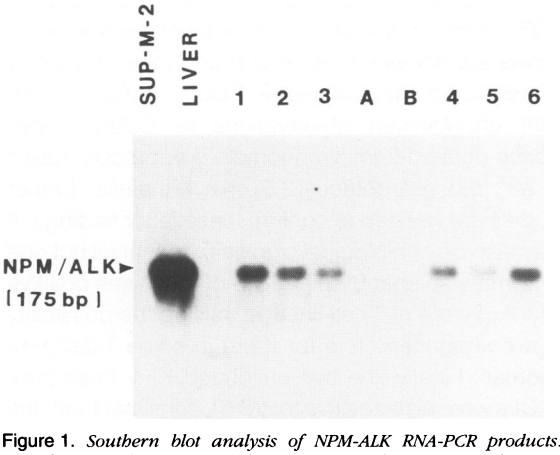

Figure 1. *Southern blot analysis of NPM-ALK RNA-PCR products. RNA from t(2;5)-positive cell line SUP-M2 and patient samples were analyzed. The 6 t(2;5)-positive patients, 3 Caucasian cases (1 to 3), and 3 Asian cases (4 to 6) are demonstrated by a 175-bp NPM-ALK fusion product. Two t(2;5)-negative Caucasian patient samples (A and B) are shown at center right. RNA from t(2;5)-negative normal liver was included as negative control.*

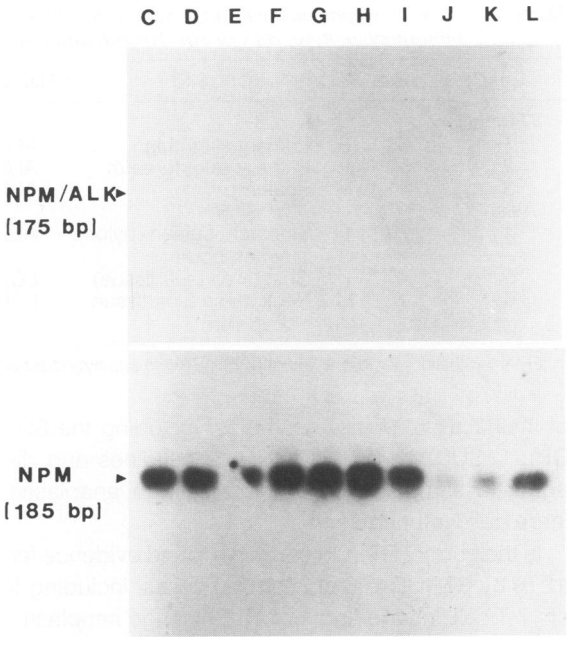

Figure 2. *Southern blot analysis of NPM-ALK and NPM RNA-PCR products. NPM-ALK RNA-PCR products are absent in t(2;5)-negative Caucasian patient samples (C to L). The 185-bp NPM product demonstrates the preservation of RNA in the NPM region.*

Discussion

The close association of consistent chromosomal abnormalities with lymphomas that have distinct morphological and clinical features is well established.[27–29] To further investigate the association of the 2;5 translocation with CD30+ lymphomas, we analyzed 37 formalin-fixed, paraffin-embedded specimens of CD30+ lymphoma from American and Hong Kong patients by RT-PCR for t(2;5). The t(2;5) translocation has been shown to fuse the NPM nucleolar phosphoprotein gene on chromosome 5q35 to the catalytic domain of anaplastic lymphoma kinase (ALK) on chromosome 2p23. It has been postulated that deregulation of the truncated ALK may contribute to malignant transformation.[25] Morris and co-workers have found RT-PCR results to correlate well with karyotypic analysis of t(2;5). Identical NPM-ALK junction sequences were found in the RNAs of all

Table 1. *$CD30^+$ Lymphomas with a t(2;5) Translocation: Clinical Features, Sites of Involvement at Presentation, Histology, Immunophenotype, and in Situ Hybridization for EBV*

Case	Age	Sex	Site	Histology	CD45	CD20	CD43/CD45RO	EMA	Lineage	ISH-EBV
Caucasian										
1	68	F	Primary skin, thigh	ALCL	+	–	+	–	T	–
2	52	M	Primary skin, forearm	ALCL	+	–	+	+	T	–
3	41	M	Spleen	ALCL	+	+	–	–	B	–
Asian										
4	79	F	Stomach, spleen, pyloric lymph node	ALCL	+	–	+	+	T	+
5	1	F	Chest wall (soft tissue)	LCL	+	–	+	+	T	–
6	8	M	Neck mass (soft tissue and skin)	LCL	+	–	+	–	T	–

EMA, epithelial membrane antigen; ISH-EBV, *in situ* hybridization for EBV EBER-1 RNA.[25]

of their 7 t(2;5)-positive samples, including the SU-DHL-1, SUP-M2, and UCONN-L2 cell lines and diagnostic samples from 4 patients with anaplastic large cell lymphomas.[24]

In the current RT-PCR study, we found evidence for t(2;5) by RT-PCR in 6 of 37 (16%) cases, including 5 of 17 T-cell lineage and 1 of 15 B-lineage neoplasm. Only 4 of 34 cases of ALCL (12%), including 2 cases of primary cutaneous $CD30^+$ T-cell ALCL and 2 cases with splenic involvement (1 T-cell and 1 B-cell), were found to have a 2;5 translocation. The remaining two cases with the 2;5 translocation were childhood $CD30^+$ T-cell LCL cases from Hong Kong involving the soft tissues and skin of the chest wall or the neck (Table 1). Thus, our results do not support the hypothesis that there is a strong relationship between the t(2;5) and $CD30^+$ lymphomas, at least in our adult-dominated series. We cannot, however, rule out the possibility that t(2;5) may still be highly associated with $CD30^+$ pediatric lymphomas, since 2 of 3 childhood cases of $CD30^+$ lymphoma in this series were positive for t(2;5). However, our results are similar to the recent study of Bullrich et al,[30] who were able to demonstrate NPM gene rearrangements by Southern blotting in only 2 of 16 (13%) cases of $CD30^+$ ALCL.

It is conceivable that our low overall rate of positivity for t(2;5) in $CD30^+$ lymphomas is due to break points occurring outside of the regions spanned by the PCR primers chosen by us. However, the preliminary work of Morris and colleagues suggests that the large majority, if not all, of t(2;5) occurring in ALCL do occur within this region. Another possibility is that our RT-PCR protocol is less sensitive than the nested RT-PCR methodology of Morris and colleagues.[31] We chose not to use nested RT-PCR for our study in an effort to minimize the chance of contamination. Nonetheless, our sensitivity derived by mixing experiments was demonstrated to be at least 1 in 1,000,000 cells in mixing experiments (data not shown), well above the number of lymphoma cells seen in the histological sections. Adequate preservation of viable RNA within the paraffin blocks was confirmed in all cases by the presence of a 185-bp NPM RT-PCR product.

Several cytogenetic abnormalities other than t(2;5) have been reported in $CD30^+$ lymphomas, including t(5;6) in $CD30^+$ LCL,[15,32] t(3;5) in ALCL,[12] a three-way translocation t(2;5;13) in LCL,[5] break points at 14q32 and 2p12 in B-cell ALCL,[22] and a monosomy 5 in ALCL.[19] It is therefore conceivable that $CD30^+$ LCL or ALCL show heterogeneous patterns of chromosomal abnormalities involving chromosome 5. Nonetheless, the high rate of t(2;5) observed in previous studies[11–18] may be a reflection of selected and small series being analyzed.

It may be of interest that two of the t(2;5)-positive cases were primary cutaneous $CD30^+$ ALCL. These latter neoplasms have been shown to have spontaneous regression in a significant proportion of cases,[33,34] although this information is lacking for our cases. It would be important to investigate whether the presence or absence of t(2;5) is correlated with a tendency for spontaneous regression. Similarly, it would be of interest to investigate the presence of t(2;5) in lymphomatoid papulosis, since it is another $CD30^+$ lymphoproliferative disorder of the skin which shows spontaneous regression and may be closely related to primary cutaneous $CD30^+$ ALCL.[35] In recent unpublished observations of $CD30^+$ T-cell clones derived from lymphomatoid papulosis, Kadin et al[36] did not detect t(2;5). Nevertheless, further studies are needed to confirm these latter findings. It may also be of biological significance that all but one (a primary splenic B-cell ALCL) of the cases positive for t(2;5) were of T-cell lineage, raising the possibility of a pathogenetic role for t(2;5) in some T-cell lymphomas. Finally, the two childhood Ki-1 T-cell non-ALCLs were also positive for t(2;5), consistent with the hypothesis that t(2;5) may be more specific for $CD30^+$ neoplasms in general than for ALCL.[15,17]

Geographic, cultural, or genetic influences did not appear to play a role in the strength of the association between $CD30^+$ lymphomas and t(2;5), since equal

numbers of American and Hong Kong cases were found to be positive. Virological factors also did not appear to play a role, as there were no significant differences in the rate of t(2;5) among EBV-positive and EBV-negative cases.

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